Optimal front line treatment for European patients harboring *EGFR* mutations: Do longitude and race make a difference?

Lorenza Landi, Federico Cappuzzo

Istituto Toscano Tumori, Ospedale Civile, Viale Alfieri 36, 57100 Livorno, Italy

J Thorac Dis 2012;4(2):226-228. DOI: 10.3978/j.issn.2072-1439.2012.03.14

For decades oncologists have been convinced that advanced non-small-cell-lung cancer (NSCLC) was a unique disease with an invariable rapid progression and with platinum based chemotherapy as the only available option for metastatic patients with acceptable performance status. During the past few years, the better knowledge of molecular mechanisms underlying this lethal disease moved researchers to leave this nihilistic attitude in favor of a positive perspective. This is the case of the Epidermal Growth Factor Receptor (*EGFR*) and its activating mutations, mainly represented by deletion in exon 19 or the L858R substitution in exon 21. Today we know that *EGFR* status assessment is mandatory before starting first line therapy and that the only presence of certain clinical characteristics initially associated with sensitivity to *EGFR*-TKIs (1)- i.e. female gender, never smoker, Asian race and adenocarcinoma histology - is not sufficient in selecting patients candidate to such treatments (2).

From a practical point of view, in our daily clinical practice, we can dichotomise metastatic NSCLC patients in two groups according to *EGFR* status: on one hand those without *EGFR* mutations - also named "*EGFR* wild type"- and on the other hand those harboring *EGFR* mutations. For the first group, standard platinum based chemotherapy, with pemetrexed and bevacizumab for adenocarcinoma and a combination of cisplatin and gemcitabine or taxanes or vinorelbine for squamous cell carcinoma, continues to be the gold standard of treatment. Furthermore, two recent phase III trials, comparing erlotinib with chemotherapy as first line treatment in unselected and treatment-naive patients, clearly demonstrated that offering an *EGFR* TKI as front line therapy without any assessment of *EGFR* status translated into a detrimental effect on patient survival (3,4).

Vice versa, if we consider *EGFR* mutant patients, the best treatment option as front line therapy is *EGFR* TKIs, while platinum based chemotherapy could be a valid option as salvage therapy at the time of progression of disease. Five large randomized phase III clinical trials, conducted in more than 1,100 Asian patients with *EGFR* mutant NSCLC, have demonstrated that the best front-line therapy for these subjects is a tyrosine kinase inhibitor (TKI), such as Gefitinib or Erlotinib (2,5-10). The FIRST SIGNAL was a trial enrolling 313 Korean NSCLC patients with the primary end point of superiority of first-line gefitinib versus standard platinum-doublet chemotherapy in never smokers and adenocarcinomas (5). The study failed to demonstrated a survival advantage for gefitinib in unselected population (22.3 versus 22.9 months; HR 0.932, 95% CI 0.716-1.213; P=0.0640), although patients with *EGFR* mutations in the chemotherapy arm had lower PFS that those receiving gefitinib. The Iressa Pan-Asia Study (IPASS) randomized 1,217 patients with adenocarcinoma and unknown *EGFR* status to receive front line gefitinib or four cycles of carboplatin-paclitaxel (2). In the subgroup analysis of the 261 patients with proven *EGFR* mutations, a statistically significant improvement in PFS emerged for patients receiving gefitinib (PFS 9.5 versus 6.3 months; HR 0.48, 95% CI 0.36-0.64; P<0.001). Conversely, gefinitib treatment was detrimental in *EGFR* wild type patients (HR for progression or death 2.85; 95% CI 2.05-3.98; P<0.001). The WJTOG 3405 trial randomly assigned only *EGFR* mutant patients to gefitinib monotherapy or to four cycles of cisplatin-docetaxel (6). Subjects receiving gefitinib had longer PFS than did those in chemotherapy arm (9.2 versus 6.3 months; HR 0.49, 95% CI 0.34-0.71; P<0.001). In the NEJ002 trial, in which patients with *EGFR* mutations were randomly allocated to first line gefitinib or to four cycles of standard carboplatin-paclitaxel, treatment with gefitinib doubled PFS (10.8 versus 5.4 months; HR 0.30, 95% CI 0.22-0.41; P<0.001) (7). More recently, Zhou and colleagues published the results of the OPTIMAL trial, a phase III study comparing erlotinib monotherapy with carboplatin-gemcitabine in Chinese *EGFR* mutant patients (8). An impressive HR of 0.16 (95% CI 0.10-0.26) for PFS was reported for subjects allocated to experimental arm (median 13.1 months for erlotinib versus

No potential conflict of interest.

Corresponding to: Federico Cappuzzo, MD. Istituto Toscano Tumori, Ospedale Civile di Livorno, Viale Alfieri 36, 57100 Livorno, Italy. Tel: +390586223189; Fax: +390586223457. Email: f.cappuzzo@gmail.com.

Submitted Mar 12, 2012. Accepted for publication Mar 19, 2012.
Available at www.jthoracdis.com

ISSN: 2072-1439

4.6 months for standard chemotherapy). Nevertheless, the huge difference in outcome between *EGFR*-TKI therapy and chemotherapy was related to unexpected low performance of the chemotherapy arm. Moreover, the chemotherapy regimen chosen as standard arm, the absence of an independent tumor response revision and, last but not least, the fact that investigators were informed that patients were all *EGFR* mutated could impacted on study results.

A topic question is if it is possible to translate these findings to European population. In fact we know that some differences exist between Asian and European patients: incidence of *EGFR* mutations is lower at our longitude and sensitivity to both chemotherapy and anti-*EGFR* TKIs seems not to be the same. This might simply reflect a different tumor biology or a different genetic make-up of the host.

In 2009, Rosell and colleagues published the results of a prospective trial designed with the aim to evaluate the feasibility of a large-scale screening for *EGFR* mutations in Spanish patients with metastatic NSCLC (9). According to trial design patients with proven activating *EGFR* mutations were considered for erlotinib, as first or subsequent line of treatment. Overall, 2,105 patients with advanced NSCLC from 129 centers were prospectively tested. Mutations were detected in 350 subjects (16%), mostly women, never smokers and with adenocarcinomas; of them, 217 received erlotinib treatment as first- (113 patients) or second-third line therapy (104 patients). Median PFS was 14 months, quite similar to than previously reported in Asian population. Two other important issues derived from this work: first, *EGFR* screening was feasible with laboratory results available in a reasonable time of seven days; second, testing *EGFR* mutations before starting therapy guided treatment choice.

In a recent issue of Lancet Oncology, the same authors (10) reported the final results of EURTAC trial, the first phase III study comparing erlotinib versus standard platinum-based chemotherapy as first line treatment in European patients with NSCLC harboring *EGFR* mutations. The study, enrolling 173 patients, met its primary end point of PFS. Patients treated with erlotinib had a 63% relative reduction in risk of progression compared with those receiving standard chemotherapy (9.7 versus 5.2 months, HR 0.37). Treatment with erlotinib was also associated with higher response rate (58% versus 15%, ITT population) and better toxicity profile. Notably, the subset analyses confirmed a significant PFS benefit in favor of erlotinib arm independently of age (>65 versus <65 years), gender, performance status (EGOG PS 0 versus 1 versus 2) and histology (adenocarcinoma versus other histologies). Subgroup analyses according to smoking status showed that the impact of the treatment was minimal in former smokers compared to current or never smokers in terms of PFS. This finding was unexpected and not in agreement with previous studies. In the OPTIMAL trial, as well as in WJTOG3405 and NEJ002 studies, both current and former smokers - even if evaluated as a single subgroup - had longer PFS when treated with TKIs. Similarly in the IPASS trial, in which eligible patients had to be never or light former smokers, no difference in PFS was seen between the two groups. It is not possible to exclude that the higher PFS benefit observed in the EURTAC trial in smokers versus former smokers was obtained by chance because of the very small number of patients included in these two subgroups.

Finally, it is important to highlight that in none of the above mentioned trials, the improvement in PFS translated in a significant advantage in overall survival in favor of gefitinib or erlotinib therapy for patients harboring *EGFR* mutations. In such trials in fact, the vast majority of patients assigned to the chemotherapy arm received an *EGFR*-TKI as second or third-line therapy, with an inevitable confounding effect on survival results. Despite this, in all trials a "clinically significant" trend in the hazard ratio for overall survival was slightly in favor of *EGFR* TKIs, reinforcing the conviction that if we consider *EGFR* mutant patients, they gain the greater benefit when an *EGFR* TKIs is administered early during the course of their disease.

In conclusion, all available data strongly support the usefulness of testing *EGFR* status in all patients with newly diagnosis of NSCLC in order to guide treatment selection and, finally, improve outcomes. In presence of *EGFR* activating mutations, front line therapy with gefitinib or erlotinib is the best therapeutic choice we can offer today to our patients, irrespective of their ethnicity. Conversely, for patients with *EGFR* wild type tumors or with unknown *EGFR* status, last generation platinum based chemotherapy still remains the standard of care.

References

1. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
2. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
3. Gridelli C, Butts C, Ciardiello F, Feld R, Gallo C, Perrone F. An international, multicenter, randomized phase III study of first-line erlotinib followed by second-line cisplatin/gemcitabine versus first-line cisplatin/gemcitabine followed by second-line erlotinib in advanced non-small-cell lung cancer: treatment rationale and protocol dynamics of the TORCH trial. Clin Lung Cancer 2008;9:235-8.
4. Thomas M, Reuss A, Fischer JR, Andreas S, Kortsik C, Grah C, et al. Innovations: Randomized phase II trial of erlotinib (E)/bevacizumab (B) compared with cisplatin (P)/gemcitabine (G) plus B in first-line treatment of advanced nonsquamous (NS) non-small cell lung cancer (NSCLC). J Clin Oncol 2011;29:(Abstrct 7504).
5. Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT, et al. First-SIGNAL:

First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung. J Clin Oncol 2012. [Epub ahead of print]
6. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
7. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
8. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
9. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958-67.
10. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-246.

Cite this article as: Landi L, Cappuzzo F. Optimal front line treatment for European patients harboring *EGFR* mutations: Do longitude and race make a difference? J Thorac Dis 2012;4(2):226-228. DOI: 10.3978/j.issn.2072-1439.2012.03.14